BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 43, NO. 7 JULY 1967

SOME CONSIDERATIONS IN THE THERAPY OF PINEAL TUMORS

*Rudolf Virchow Lecture**

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THE 100 years of the 19th century are, medically speaking, in many ways like the legendary days of old. Not because of their remoteness in point of time—I was born in the 19th century myself—but because giants such as Pasteur, Koch, Lister, and Rudolf Virchow walked the earth. To state that Virchow is, even today, a three-dimensional figure would be to neglect at least half a dozen other dimensions of his richly endowed personality. He was physician, pathologist, epidemiologist, anthropologist, archeologist, sociologist, historian, linguist, political scientist, and practicing politician. And he stood in the top rank of each of these disciplines.

As a very young man he set his goal as "an all-around knowledge of nature from the deity down to the stone." What is more, his great mind, coupled with his small but rugged physique, unbounded energy, and a

*Based on a lecture given before the Rudolph Virchow Medical Society in the Ctiy of New York at a meeting held at The New York Academy of Medicine, October 3, 1966. By special arrangement this paper will also appear in the *Proceedings of the Rudolf Virchow Medical Society in the City of New York.*

long life, permitted him to come very close to achieving his aim.

His productivity is not only astonishing, it is almost unbelievable. Ackerknecht[1] states:

> Besides his research, crystallized in more than two-thousand papers and books, besides his academic and popular teaching, his traveling, his political and administrative work, besides his editorial and organizational activities, he still found time to arrange and label with his own hands more than twenty-thousand preparations and four-thousand skulls for his Institute collection.

Politically he was always on the side of liberalism, and he even helped man the barricades in the unsuccessful German revolution of 1848. After a period of quiescence, he reentered the political arena as a member of Parliament and was such a goad in the side of Bismarck that the chancellor actually challenged him to a duel. One cannot help thinking, when visualizing such an encounter between the spunky little *Geheimrat* and the "Iron" Chancellor, of David and Goliath. Only this time no miracle from heaven could have saved the miniature defendant, for Virchow—David—was an atheist or at least an agnostic and certainly did not believe in heaven. However, he averted the disaster in his own forthright way. He simply refused to fight—with swords, that is.

While Virchow is best known to us as the discoverer of cellular pathology, he was responsible for so many discoveries in morphological as well as physiological pathology that it is not at all surprising to find that he was also the first to describe the appearance of tumors in the region of the pineal body, which is the subject of this lecture. His report on these lesions largely reflects the doubts and uncertainties still existing concerning them today.

In his famous book, *Die krankhaften Geschwülste*,[30] he states (the translation is mine):

> I add here a type of tumor, namely the hyperplasia of the pineal; I cannot decide whether it is to be considered, in the narrowest sense, a glioma. In view of our lack of knowledge of the function of this organ and its parts, I cannot draw any firm conclusion as to whether the increase in these elements should not rather be classed with the neuromas. I can state nevertheless that some gliomas of the brain highly resemble the hyperplastic tumors of the pineal grossly and in their individual elements. No one, to my knowledge, has ever estimated the neuronal nature of the pineal cells.

Indeed, no firm concept of the function of the pineal body exists to this day.

In a recent review entitled "The Pineal Gland," Richard Relkin[23] pointed out that in fishes, amphibians, and lacertilian reptiles the pineal gland is primarily a photoreceptor organ in which distinct sensory cells resembling retinal cone cells are found. In mammals there are no sensory cells, the pinealocyte being a secretory cell.

As for proof concerning its secretory activity, neither extirpatory experiments nor experiments in which there were injections of pineal extracts or implants of pineal tissue have given clear-cut answers.

The consensus is that the pineal secretes an inhibitory hormone causing retardation of sexual maturation until puberty, when the gland atrophies and the maturing secretions of the pituitary, adrenal, and gonadal glands go into high gear. These impressions are derived from the rare clinical cases in prepubertal male children with tumors in the pineal region who develop macrogenitosomia praecox, whereas occasional cases also having tumors in this location are associated with delayed puberty. Correlations of such clinical manifestations with this type of tumor tend to show that parenchymatous pineal tumors display a high degree of association with depressed gonadal function, whereas nonparenchymatous lesions such as gliomas, or those teratomas that destroy the normal pineal and contain no neoplastic pineal tissue may be associated with pubertas praecox. Thus, according to this theory, pineal hyperfunction is associated with delayed pubescence, and hypofunction with advanced puberty. However, this is still a highly theoretical concept.

Moreover, Virchow's confusion derived not only from a lack of knowledge concerning the function of the pineal, but also from the considerable variation in the microscopic appearance of these tumors.

When Bailey and Cushing[4] presented their work on the *Classification of the Tumors of the Glioma Group on a Histogenetic Basis* in their classical monograph in 1926, they included eight cases of pineal tumor, three of which they named pineoblastoma, and five pinealoma. As time passed, this proved to be an oversimplification, and it failed to cover a number of tumors in this region clearly not eligible for such classification. Thus Bochner and Scarff[5] described a teratomatous lesion of the pineal containing elements from all three embryonal layers, including fully developed teeth, as well as pineal tissue. This tumor was

primary in the pineal region, and they theorized that there is "inherent multipotentiality in the primitive cells of the pineal body similar to that found in the cells of the testes and ovary." However, as late as 1941, Globus[10] still clung to the histogenetic origin of these tumors and felt that he was able to match each of the 12 cases he reported with some stage in the histogenesis of the pineal. It is important to note, by the way, that Globus found the majority of the tumors on which he reported to be invasive lesions.

It remained for Dorothy Russell[25] to point out in 1944 that the resemblance of the so-called pinealomas to embryonic pineal tissue is only superficial and is suggested by their mosaiclike appearance. The large spheroidal cells so conspicuous in this tumor, unlike similar cells in the embryonic pineal body, lack the blepharoblasts and the silver-staining qualities of these cells, while the smaller cells of the tumor are really only smaller examples of the spheroidal cells, and not lymphocites. Moreover, in two of Dr. Russell's cases, which were studied in serial sections, she found teratoid elements, and she felt that those neoplasms making up the majority of pineal tumors that Bailey, and also Globus, had called pinealomas, are really atypical teratomas resembling the spheroid-cell carcinomas of the testes. As further proof of the independence of these tumors from the pineal, she called attention to the occurrence of these very tumors in other sites along the midline structures of the brain, such as the hypothalamus, the so-called "ectopic pinealomas." In such cases a perfectly normal pineal body is usually found in the normal anatomic position. This is not to say that true pinealomas do not occur but, in her opinion, they are very rare.

Horrax and Wyatt,[16] however, reported in 1947 three cases of "ectopic pinealoma," in one of which they demonstrated (and in a second one they presumed) a continuity of the tumor with that in the original site in the region of the pineal, with extension to the hypothalamus by way of the lateral walls of the third ventricle. The third case, however, was definitely primary in the neighborhood of the optic chiasm.

In 1949, Walton[31] reported two cases of teratomas in the hypothalamic region that contained pineal tissue. This he felt was due to the polypotentiality of these tumors. He argued, then, that they should thus be called teratomas in the hypothalamus, rather than ectopic pinealomas; with this opinion I am inclined to agree.

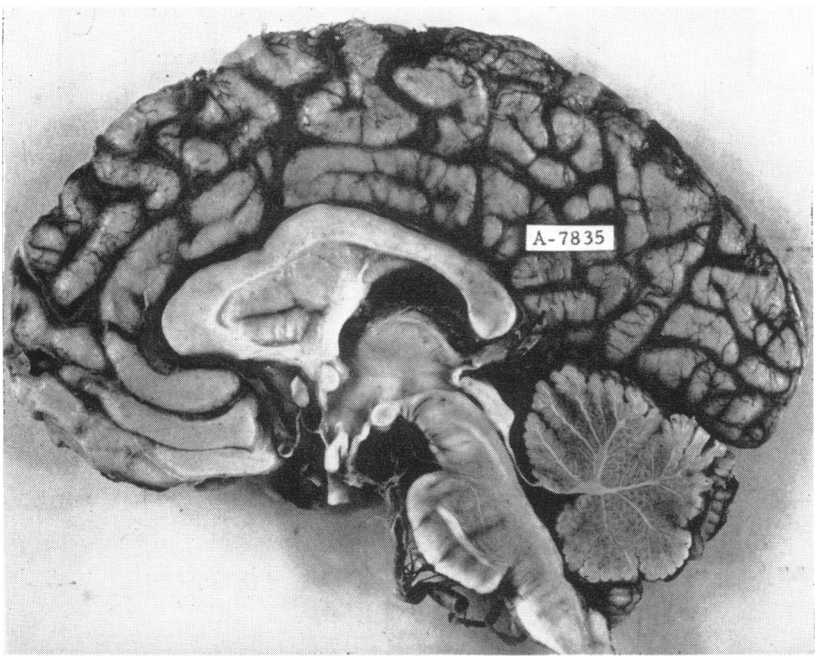

Fig. 1. Midsagittal section of a normal brain, showing the relation of the pineal body to the quadrigeminal plate and the latter's relation to the aqueduct of Sylvius.

In 1957 Løken[19] described three cases of tumor in the hypothalamic region, all of them histologically resembling Russell's atypical teratomas.

Russell's thesis was strongly supported by N. B. Friedman[9] in 1947, when he reported on his study of 23 cases of pineal tumor found in the collection of the Armed Forces Institute of Pathology, Washington, D.C. Ten of these, identical in appearance with the spheroid cell carcinoma of the testes—thus the atypical teratoma of Russell, Friedman felt, could as well be called "seminoma" or "germinoma." Five others were true teratomas, or teratomatous carcinomas, and eight were gliomas. Friedman's observation that the germinoma is extraordinarily sensitive to radiation will find support when we come to a discussion of the treatment of these neoplasms.

This brief discussion by no means covers all the possible types of tumors in the pineal region, nor the extensive literature on this aspect of the problem, since it is my purpose on this occasion to concentrate primarily on the *treatment* of these rare but interesting neoplasms.

For the same reason we need not tarry very long on the diagnosis.

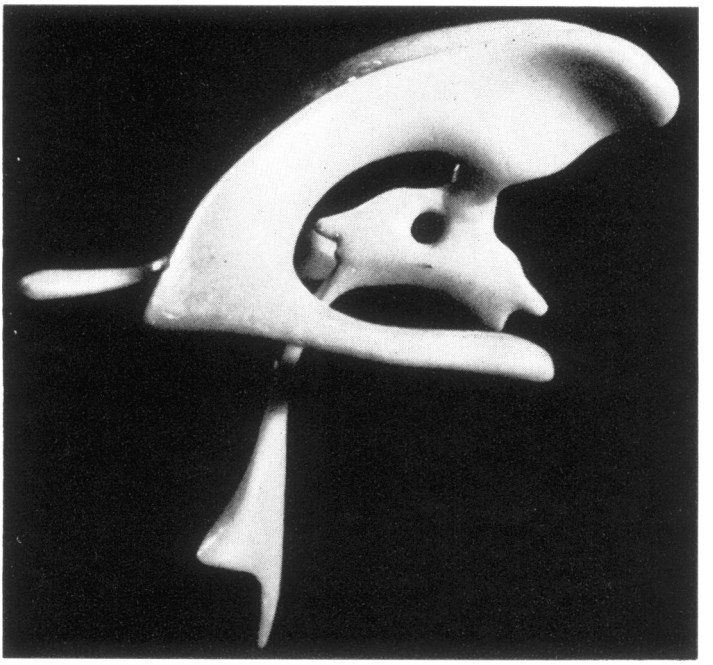

Fig. 2. A mold of the cerebral ventricular system, graphically presenting the possibility of a "bottleneck" in the aqueductal region.

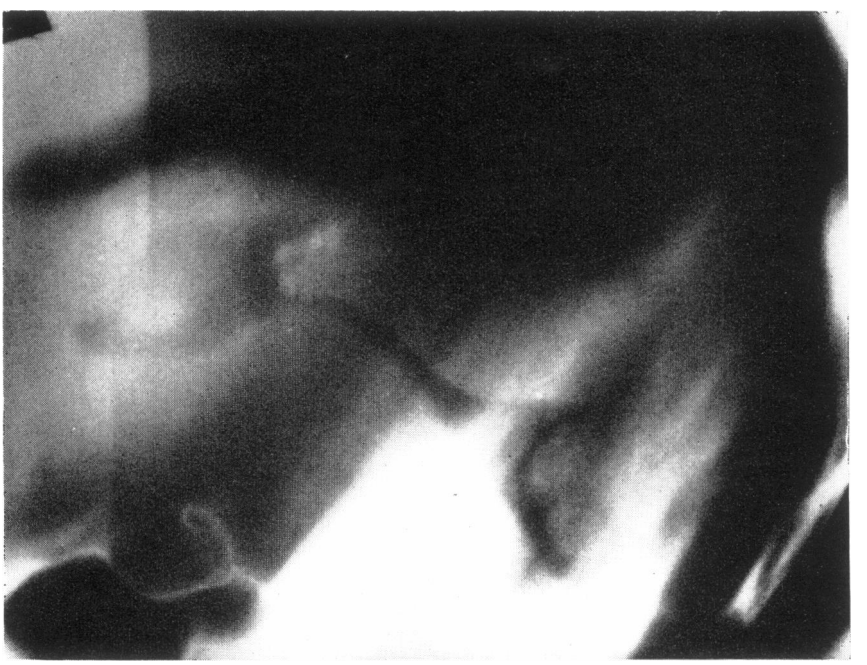

Fig. 3. Autolaminagram of gas-filled ventricles in a normal individual. This shows the unobstructed aqueduct of Sylvius in its normal relation to the third and fourth cerebral ventricles.

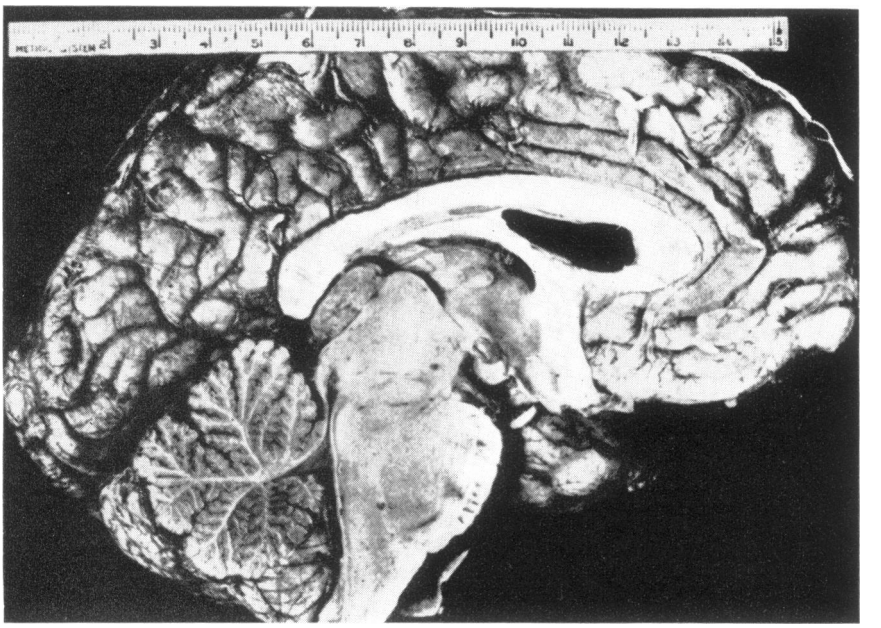

Fig. 4. Sagittal section of brain in a case with a small tumor in the pineal region, showing already the obliteration of the aqueduct and the dilatation of the third ventricle. Reproduced by permission from Horrax, G., and Bailey, P. Pineal pathology: Further studies, *Arch. Neurol. Psychiat. 19*:394-415, 1928.

The major point about the clinical aspect of the problem is to remember that the pineal body is located just above the quadrigeminal plate, and that the quadrigeminal plate forms the roof of the aqueduct of Sylvius. Figure 1 shows a sagittal section of a normal brain. Here one sees that the cavity of the lateral ventricle is hidden by the septum pellucidum, but its outlet into the anterior part of the third ventricle by way of the foramen of Monro is clearly visible. The cerebral fluid then passes backward and leaves the third ventricle via the aqueduct of Sylvius. The quadrigeminal plate is well seen here, and also the pineal above it. After passing into the fourth ventricle by way of an unobstructed aqueduct, the fluid leaves the fourth chamber by way of the foramina of Magendie and Luschka and passes into the subarachnoid spaces, to bathe the base and the convexities of the cerebral hemispheres and then to be reabsorbed into the general blood circulation through the arachnoidal villi. Figure 2 shows the lateral view of a mold of the cerebral ventricular system, which graphically presents the relatively narrow aqueduct. Figure 3 shows a lateral laminagraphic ventriculogram of this area as it appears in a normal individual. Since the lumen

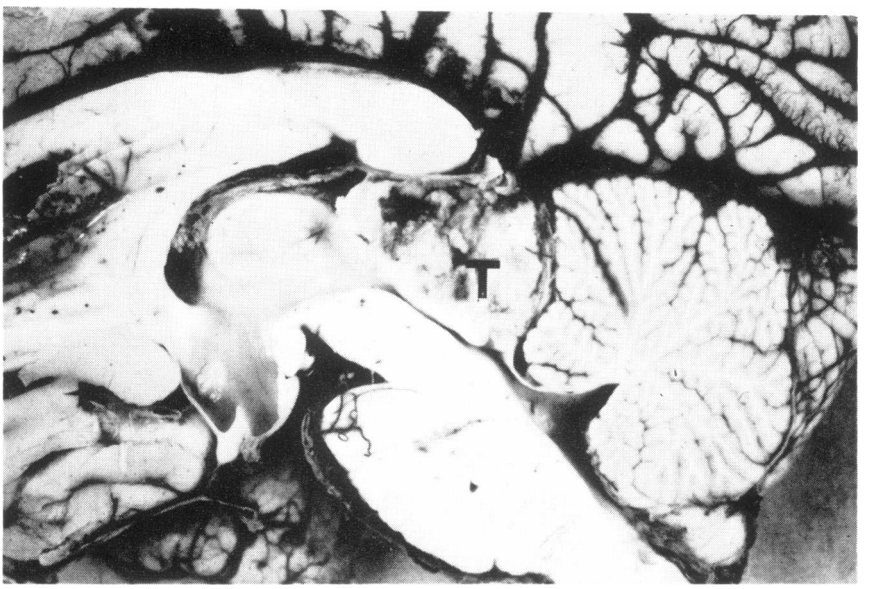

Fig. 5. Midsagittal section of the brain in a case of a large pineal tumor (T). The third ventricle is ballooned out, and the lamina terminalis is almost paper-thin.

of this narrow aqueductal passageway varies in the diameter of its cross-section from only 1 mm. to 3 mm., it is easy to see how any—even a minor—degree of pressure on the roof would obstruct the passageway and produce obstructive hydrocephalus. Now see, in Figure 4, what happens when even a small tumor occupies the region of the pineal. The fluid meets a block at the aqueduct, and the ventricular system ahead of the block dilates like an artificial lake behind a dam. Note particularly the stretching of the anterior wall of the third ventricle. Figure 5 shows a sagittal section through a brain specimen harboring a larger pineal tumor. I call your attention to the even greater thinning-out of the lamina terminalis. And Figure 6 shows how it looks when the brain specimen is x-rayed. Note how the tumor, which is denser than the surrounding brain because of calcium deposited in it, bulges into the posterior border of the third ventricle. The next, Figure 7, represents the lateral ventriculogram made during life in this patient, in which the characteristic deformity may again be noted.

Anyone would deduce from all this that the symptoms and signs of tumors in the region of the pineal would necessarily fall into four broad categories: 1) those of increased intracranial pressure due to obstructive hydrocephalus; 2) those of interference with the function

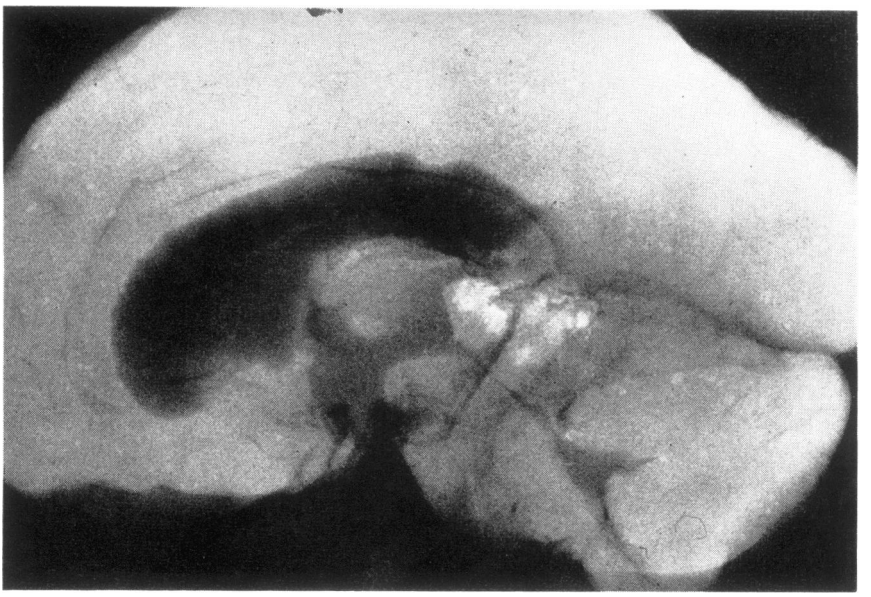

Fig. 6. Same case as in Figure 5. A roentgenogram of the brain, postmortem, showing the ballooned-out third ventricle, and the thin, elongated aqueduct of Sylvius.

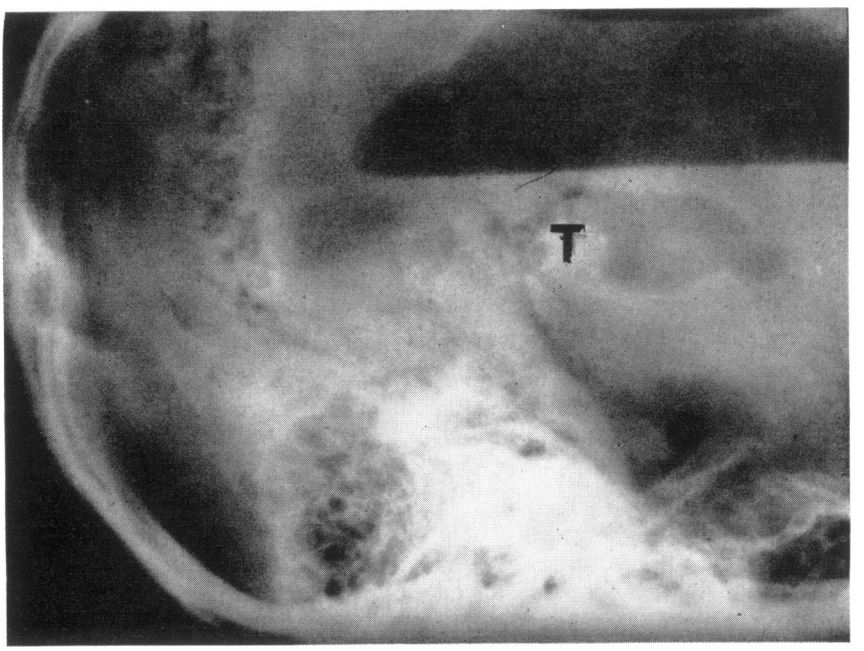

Fig. 7. Same case as in Figures 5 and 6. This shows the indentation by the tumor (T) into the posterior border of the third ventricle.

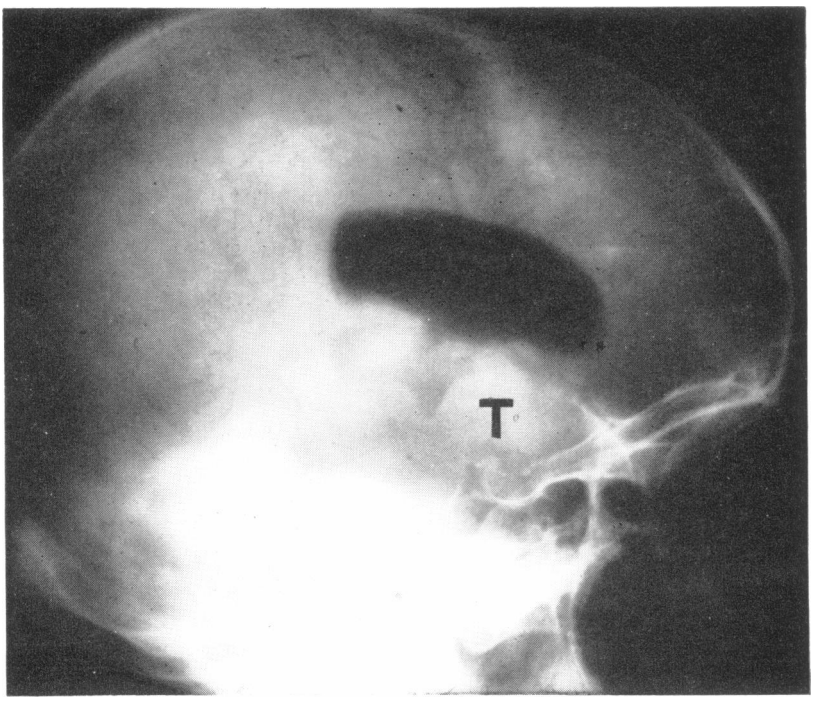

Fig. 8. Lateral ventriculogram, brow-up position, showing the indentation of the anterior border of the third ventricle by a tumor (T) at the foramen of Monro.

of the quadrigeminal plate and the midbrain generally; 3) those of interference with the function of distant parts of the brain, such as the hypothalamic-pituitary region; and 4) those less-well-understood endocrine manifestations due to depression or hyperactivity of pineal secretion, if any.

Since it has also been observed that the majority of patients with this disease are young males, a theoretical classical case—which, by the way, almost never happens—therefore would be that of a boy, let us say 8 years of age, complaining of severe headache and vomiting. He may also be suffering from double vision, and may have been observed to be partially deaf, unsteady of gait, and spastic. If, on examination, he proves to have a cracked-pot sound on percussion of his head (Macewen sign), due to spreading of the cranial sutures; papilledema; extraocular muscle disturbances, particularly limitation of upward gaze; pupils that respond poorly to light; partial or complete deafness; cerebellar ataxia and bilateral Babinski signs; and if, in addition to all this, he shows signs of advanced gonadal maturation, the presumptive diag-

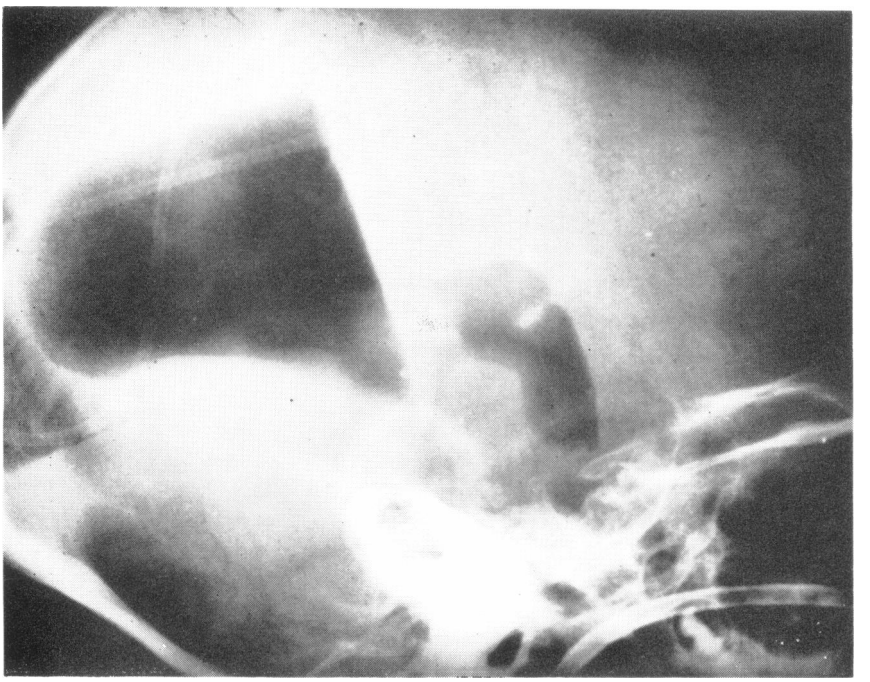

Fig. 9. Lateral ventriculogram, brow-down position, outlining dilatation and anterior angulation of the aqueduct of Sylvius resulting from a tumor of the cerebellum.

nosis of tumor in the pineal region will almost certainly prove to be correct. Unfortunately for the clinician, it almost never happens that way. Clinically, pubertas praecox is a rare accompaniment of pineal tumor, and signs of increased intracranial pressure plus cerebellar dysfunction are most prominent. Thus, especially in preventriculography days, these cases were frequently mistaken for tumors in the cerebellum. What is more, exploration of the posterior fossa not only failed to reveal the lesion, but was often followed by death.

Ventriculography has largely eliminated this uncertainty. And this diagnostic procedure, with due precautions into which I need not go, should be carried out in almost any case in which increased intracranial pressure due to obstructive hydrocephalus is encountered. This would include cases with tumors of the anterior third ventricle obstructing the foramen of Monro, tumors in the region of the pineal that we are chiefly concerned with here, and tumors in the posterior fossa obstructing the inlet of, or the outlet from, the fourth ventricle.

Figure 8 is from a lateral ventriculogram in a case of tumor of the anterior part of the third ventricle. Note that the foramen of Monro is

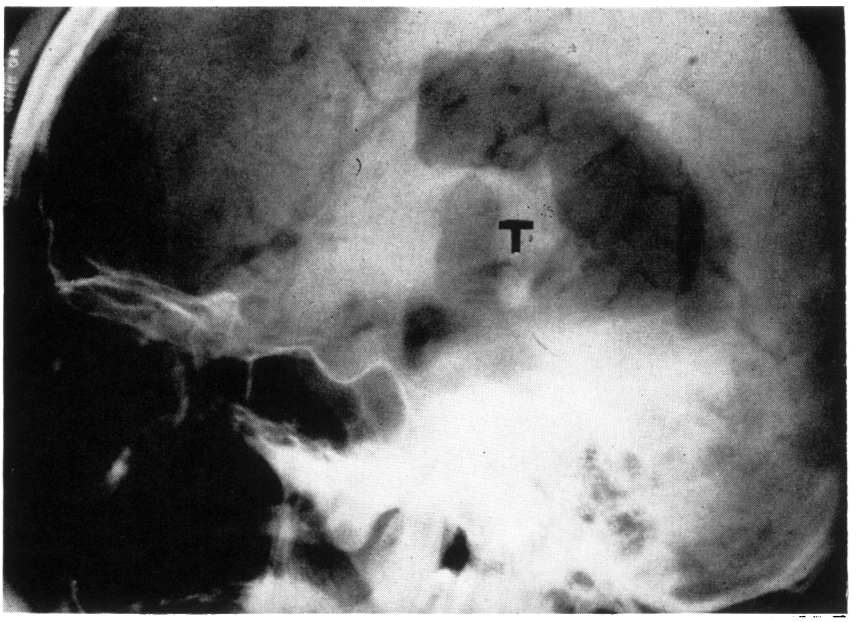

Fig. 10. Lateral ventriculogram, brow-down position, from another case of tumor of the pineal. The third ventricle is dilated and indented posteriorly by the tumor (T), and the aqueduct is not visualized.

dilated, and that the gas in the dilated third ventricle shows a projection of tumor into it on its anterior border. The next view, Figure 9 in this group, is from a patient with a cerebellar tumor. Here the whole of the dilated third ventricle is visualized, but the aqueduct is also dilated, and its caudal end is kinked forward by the forward thrust of the tumor in the posterior fossa.

Contrast this with the next illustration, Figure 10, from another patient with a tumor of the pineal, to which I again call your attention. The lateral ventricles, the foramen of Monro, and the *anterior* portion of the third ventricle are all dilated, and the outline of the tumor is seen projecting into its posterior border.

In any case in which a midline tumor obstructing the free passage of cerebrospinal fluid is suspected, and the ventriculograms show the protrusion of a mass into the posterior border of the third ventricle such as this, a diagnosis of tumor of the pineal region is justified and is most likely to be correct.

So much for the diagnosis.

We come now to the question of treatment, which is my point of emphasis on this occasion. Before doing so, however, let us stop for a

moment to gain perspective. Brain tumors in general are relatively rare lesions, making up only 0.06 to 0.15 per cent of all the causes of death. Moreover, pineal tumors are rare tumors among the already rare intracranial tumors, making up only 0.4 to 1.0 per cent of intracranial neoplasms.

Why, then, have I chosen to present, before a general medical audience, a discussion involving technical neurosurgical problems, matters of neurosurgical judgment, and related radiotherapeutic considerations in so rare, limited, and highly specialized an area of medical interest? Indeed, I do so with apologies to all of you. However, certain principles and philosophical concepts of therapy are involved here that are equally valid in many other situations in the treatment of human ills, and they make this discussion—so, at least, I hope—worthy of your time and attention.

I can still remember many a doctor's consulting room, a few generations ago, conspicuously displaying the framed motto: "*Primum Non Nocere.*" While Latin is no longer the common language of scholars and physicians, the principle—First of all, do no harm—should still be our guide, in whatever language we communicate.

And the direct surgical attack upon these tumors was in the past—and still is, by and large—a harmful procedure. This is due, for the most part, to two factors: first, the dangerous location of these tumors and, second, their infiltrating character, which makes it impossible to eradicate them surgically in toto, even after Scylla and Charybdis are successfully circumvented.

Since the early decades of this century, various approaches have been made to reach the lesion surgically. Thus, in 1907 Theodor Krause suggested trying to approach them through the posterior fossa, transtentorially; and Brunner, as reported by Rorschach in 1913, attempted but failed in removing a pineal tumor by this route. Puusepp in 1914 ligated the lateral sinus, divided the tentorium, and thus reached the tumor site, but the patient died in this attempt.

In 1921 Dandy,[6] who was a bold, resourceful, and skillful surgeon, exposed the parieto-occipital region of the brain on the right (that is, the nondominant) side, divided the large draining veins that passed from the cerebral cortex to empty into the superior longitudinal sinus, then retracted the hemisphere away from the falx cerebri. Upon reaching the splenium of the corpus callosum he divided this structure, and

in this way visualized the tumor through a tangle of the great vein of Galen and its tributaries. The first case, after all this, proved on exposure to be a widely infiltrating glioma which he could not even *attempt* to remove. The second case was a patient from whom he succeeded in removing a well-demarcated mass, which proved to be a tuberculoma. The patient died 8 months later, presumably from a spread of her disease to other parts of the brain. The third patient reported upon in his paper survived the operation but died 48 hours postoperatively. No wonder that 4 years later, in 1925, when Horrax and Bailey[14] reported 12 verified cases from Harvey Cushing's clinic, they had all been verified postmortem. All had ended fatally *without* operation because they had been considered inoperable.

Harvey Cushing himself, in 1926,[4] was extremely pessimistic about the future treatment of these lesions. He felt that it was improbable that we should ever be able successfully to extirpate them in view of their inaccessible position. He believed, from all points of view, that they are most unfavorable lesions.

In 1931 Van Wagenen,[29] faced with a case of pineal tumor, tried a new approach. He exposed the posterior half of the right cerebral hemisphere; entered the dilated lateral ventricle by a temporo-occipital cortical incision; then, locating the bulge produced by the tumor on the medial side of the ventricle, he transected the medial side of the brain, thus reaching the tumor. Even then he had to leave some of the tumor behind because it was so intimately involved with the great vein of Galen. Postoperatively the patient was incontinent, sluggish, and had impaired memory. These symptoms largely cleared up, and the patient received x radiation. She was followed for 15 months, when she was lost to follow-up. As a result of this experience, Van Wagenen concluded that perhaps a better way to treat these patients is to do a subtemporal decompression first, followed by roentgen irradiation; then, when recurrence of symptoms occurs, as he believed it usually would, the radical approach should be tried.

In 1932 Harris and Cairns[11] wrote up an extensive study of the diagnosis and treatment of pineal tumors, and included a report of one case operated upon by Cairns. This male patient, 20 years of age, was first mistakenly explored for a cerebellar tumor, and actually improved for 6 months. The second operation was by Dandy's method, but the right internal occipital vein had to be cut in order to get the tumor out.

The patient was conscious following removal of the tumor. However, he had a left hemiplegia, left homonymous hemianopsia, and was noisy and incontinent. These signs cleared up in about 4 weeks, but he was left with poor memory. In spite of this heroic effort, he began to show signs of a recurrence of tumor about 9 months after the operation. He was then given some radiation therapy, which was admittedly inadequate because, among other things, the patient could not be made to lie still during the treatments. Nevertheless, he showed some improvement until some months later when he fell, struck his head, and again showed progressive signs. Radiation was resumed, with the patient sedated with Nembutal for each treatment. He improved steadily and seemed to be in good condition 13 months after the operation, when the report was made.

In 1935 McLean[20] reported another fatality following radical removal of a pineal teratoma.

In 1936 Dandy[7] published another report. Since the 1921 paper, he had had seven fatalities postoperatively, then three patients that survived. Of these, one died 3 months postoperatively, cause unknown; the second survived 2 years and 6 months, and then died of a recurrence of his tumor; and the third was living 4 months postoperatively when the paper was written. In 1936 also, another paper by Horrax[12] included a report on two more cases. One patient, a middle-aged woman, survived a partial extirpation of her tumor, was given irradiation, and was doing well 18 months later. The other patient was a boy of 10 years, with pubertas praecox and a tumor located but not verified in the pineal region; he was finally doing well after having had a subtemporal decompression as well as several courses of radiation therapy.

The next year, in 1937, Kahn[17] contributed his experience with two cases of pineal tumor. One was a patient operated upon by Max Peet in 1929; the patient was still living then and had received postoperative irradiation. The second was a patient upon whom Kahn himself had operated. This patient was alive one year later, but was somewhat below par in his intellectual functions and seemed to have a permanent left homonymous hemianopsia. The year 1937 also saw another report by Horrax[13] upon a case of a patient with a huge tumor (70 g.), in which he had to resect the right occipital lobe of the brain in order to deliver the mass. The postoperative course was agonizing, and ended fatally in 3 months.

Baggenstoss and Love[3] in 1939 wrote a general report on the experience of the Mayo Clinic with pinealomas; 10 cases had been seen there in 23 years. They did not report upon early or late results of treatment, but their attitude was distinctly gloomy since they stated: "The treatment of pineal tumors carries a high mortality, and the results of therapy at present are unsatisfactory."

More than 20 years after the description by Dandy of his radical operation for pineal tumors, Horrax, who had made many studies on these lesions, reported together with Daniels[15] upon four patients with such tumors, three of whom had had only subtemporal decompression and radiation therapy, and the fourth, radiation therapy alone; all four patients had recovered and were leading useful lives 18 to 30 months after treatment.

In 1943 W. O. Russell and Ernest Sachs[26] had collected from the literature 32 cases of patients with tumors of the pineal who had been treated by direct attack upon the tumor; only three of these patients had survived the immediate postoperative period.

Toward the end of the 1940's the impact of this holocaust began to trouble even the most intrepid surgeons. Torkildsen, who in 1939 had invented a method of circumventing an obstruction to the cerebrospinal fluid by leading the stream by way of a permanent tube from a lateral ventricle into the subarachnoid space, suggested the use of this method in tumors of the pineal region. He wrote an article[28] in 1948 entitled, "Should extirpation be attempted in cases of neoplasm in or near the third ventricle of the brain?" He answered his own question in the negative, and reported on eight cases of pineal tumors treated by his shunting method. Three of these patients were living and well 7 years and 6 months, 4 years and 6 months, and 2 years respectively after operation. In the same volume of the *Journal of Neurosurgery*, Ward and Spurling[32] presented their experience with "The conservative treatment of third ventricle tumors." They had collected the cases of 14 patients with appropriate symptoms and typical ventriculograms, sufficient to make the diagnosis of a tumor in the pineal region. Each was treated with subtemporal decompression and "intensive radiation." Two of these patients failed to respond to treatment, and proved to have cysts obstructing the aqueduct. Six patients had malignant gliomas, in whom conservative treatment failed. They were then operated upon by direct approach, and were all dead within 3 years. Six patients were

alive and well approximately 6 to 16 years after subtemporal decompression and radiation therapy.

The largest experience with the surgical treatment of pineal tumors from a single institution was reported by Ringertz, Nordenstam, and Flyger[24] in 1954 from the Serafimerlasarettet in Stockholm. In a period of 25 years, from 1926 through 1951, 65 such cases had been seen, and 51 had grossly total or partial extirpation of the tumor by the Dandy technique. In addition to an immediate operative mortality of 58.8 per cent, six of the *survivors* died in less than 10 months postoperatively. Only seven patients were living 5 to 20 years postoperatively, and two of these had had only cysts instead of solid tumors.

However, as late as 1960 this radical operation was still being reported for the treatment of pineal tumors. Thus Kunicki[18] presented eight cases that year in which the Dandy procedure was used. Actually six of them survived the operation, but all showed poor memory and masklike immobility. Three had left hemiplegia, and one had left homonymous hemianopsia. The average stay in the hospital following operation was 4 months. The follow-up of the six survivors also showed many disturbing aspects. One patient, after 30 months, was attending school, but was aggressive, quarrelsome, and lacked perseverance. A second patient was blind, but was seemingly well otherwise; but he had received postoperative radiation therapy. The third patient was normal and attending school, but he too had had postoperative radiation. The fourth patient died after 6 months, cause unknown. The fifth patient was working as a farm hand 70 months postoperatively, but had also been given postoperative radiation. After 2 years of relative good health, the sixth patient died in a psychiatric hospital.

Thus we see that only in the three cases in which Kunicki was led to use postoperative irradiation did the patients do reasonably well.

At the present time so many mechanical, chemical, and electronic devices are available for our use that what was impossible only 20 years ago has become a matter of daily achievement. However, modern methods utilizing stereotactic instruments thus far have not shown any great promise, although experience is still limited. Thus, Radanowicz-Harttmann[22] reported two cases, in one of which a preliminary Torkildsen procedure was done, followed by Yttrium 90 implantation into the tumor by stereotactic means. The patient died a few days later, and the postmortem examination revealed a very large and very hemorrhagic

tumor. The second patient in whom a similar procedure was planned got only as far as the Torkildsen, and then died of a pulmonary embolus. At postmortem an ependymoma was found, with infiltration of neighboring structures.

Incidentally, both of these patients showed reactive meningitis to the tube used for the Torkildsen shunt. With the selection of minimally reactive tubing for the shunt, this complication usually can be avoided, but not always. It is one of the prices one sometimes must pay for leaving foreign material implanted in patients' bodies for an indefinite period of time.

The present official neurological attitude toward these lesions was summarized by Zülch[33] in the 1965 English edition of his book, *Brain Tumors: Their Biology and Pathology*. In this work he stated: "Operation, even 'total extirpation,' seldom insures freedom from recurrence. Besides, total removal is difficult due to the pinealomas' close relationship to nervous centers and important blood vessels, and their growth by infiltration in the marginal zone."

My Own Material

One day, about 6 months ago, while thinking about an appropriate subject for this lecture, I had a follow-up visit from a vigorous, healthy-looking, youngish man of 36 whom I had treated for a pineal tumor in 1943—that is, 23 years previously. This man had by now attended high school and college, was a successful teacher and had a family consisting of a wife and three children. It occurred to me, then, to check up on my own experience with these lesions and report to you on them on this occasion.

I found 14 cases of tumors in the pineal region in my own series that fit the diagnostic criteria already mentioned. The only exception was one patient in whom the ventriculographic studies were unsuccessful, so that the posterior border of the third ventricle was not visualized. However, he had clinical signs of increased intracranial pressure, obstructive hydrocephalus, and paralysis of upward gaze, and most likely had a pineal tumor.

Three of the 14 cases had been treated by direct approach to the tumor, and all three had died postoperatively. One of these was a 27-year-old woman upon whom I did a subtemporal decompression, which was followed by radiation. She failed to get relief, was taken to Balti-

more, Md., where Dandy removed a tumor from her pineal region, but she died in the immediate postoperative period. The second patient was a boy of 9 with macrogenitosomia praecox. I succeeded in partially removing a tumor diagnosed as "pinealoma" at the time—that was in 1936. The boy was confused and right hemiparetic after the operation, but was beginning to do well, when he managed to get his fingers under the dressing and rip his wound wide open. It was immediately resutured, but he developed fulminating meningitis and died two months after the operation. The third patient in this group was a 22-year-old girl who died 4 days after a radical removal of the tumor by the Dandy technique.

Nine of the other 11 patients were treated by perforating the thinned-out anterior wall of the third ventricle to bypass the dammed-up fluid; one had a Torkildsen procedure, and one only a subtemporal decompression. In all these patients, operation was followed by radiation therapy. One of them died 3 years and 6 months after treatment, with uncontrollable recurrence of the lesion and, eventually, multiple spinal cord implantations of tumor. Another died 16 years after treatment. The remaining 9 patients are alive, respectively 9, 10, 12, 14, 16, 18, 19, 23, and 24 years following treatment. One patient, during 9 years of follow-up, has had two recurrences of focal symptoms without recurrence of papilledema, suggesting that the shunt is working while the tumor is periodically becoming reactivated. Each time, so far, she has responded to further radiation therapy. The other eight patients are not only alive, but are functioning normally in a variety of life situations.

The history of events in one of these cases may perhaps be made a little more vivid for you by describing its progress, and I have accordingly chosen to give you the details in the case of the young man who sparked my interest in the choice of subject for this paper.

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This boy was first seen by me on September 27, 1943, when he was 13 years of age. He had been healthy until a few months previously, when he began to have severe headaches associated with vomiting. Four or five weeks before the above date, his left eye became crossed, and he complained of double vision. These symptoms were progressive, but no other neurologic symptoms could be elicited.

On examination the child was extremely uncomfortable, holding

his head and moaning. He was lethargic and uncooperative until he vomited, and then seemed a little more responsive. The right pupil was slightly larger than the left. Both reacted sluggishly to light. There was bilateral external rectus weakness. Upward gaze could not be tested because of lack of cooperation. Bilateral papilledema was noted. A suggestive left Babinski sign was recorded. The general physical examination revealed no abnormalities.

Routine blood and urine tests were all normal.

Plain x rays showed the skull to be within normal limits.

Cerebral gas ventriculograms were reported as showing: "Symmetrically dilated lateral ventricles and a dilated anterior portion of the third ventricle. There is a deformity of the posterior portion of the third ventricle characteristic of a tumor in the region of the midbrain, such as a pineal tumor."

On October 1, 1943, a right frontal craniotomy was performed, and the very thinned-out lamina terminalis was punctured. An incidental small subtemporal decompression was added for good measure.

He did extremely well postoperatively. His headaches subsided, the papilledema disappeared, and he became alert, bright, and cooperative in a matter of days.

Eleven days after the operation he was discharged from the hospital, to be treated with radiation to the tumor site on an ambulatory basis.

Between October 18, 1943, and January 21, 1944, he received three courses of x radiation, each consisting of about 1,000 r, to the tumor site.

Meanwhile he had remained symptom-free and, on examination on November 17, 1943, he looked well, had no diplopia or headaches. The decompression area was level and soft. The pupils still did not react well to light, and some limitation of upward gaze was present. The optic discs appeared to be within normal limits.

In November 1945 he again complained of mild headaches, and his optic discs showed some venous congestion. Because of this he was given an additional, similar, course of radiation therapy.

From then on to the present, I either saw him personally, or heard from him by letter, at approximately yearly intervals. In his last letter he wrote: "In answer to your letter, I am in excellent health. I have had absolutely no trouble in regard to my head. As

you may know from my previous letters, I am married and the father of two boys, with a third on the way. I am in my eleventh year of teaching. I thank you for your continued interest. . . .

Seven other patients in this group present essentially similar pictures, and the young woman previously mentioned with the 9-year follow-up after treatment, who was again having trouble, is once more responding to radiation therapy.*

Discussion

The radical surgical treatment of tumors originating in the pineal region, after 50 years more or less of bold, aggressive efforts on the part of several generations of neurosurgeons to extirpate them, is even to this day dismally unsuccessful. What the future may hold, when stereotactic methods are more skillfully used than they are today, is uncertain. I have grave doubts as to their applicability to these or, for that matter, to any other intracranial lesions that infiltrate neighboring brain structures. This would be particularly true in the region of the midbrain, where so many vital brain mechanisms are located. The reason for my skepticism is that the destructive agents that can be delivered through a probe, whether it be supercold, superheat, or a radioisotope implant, are totally necrotizing. The margin between the zone of necrosis and the neighboring brain would have to be so exquisitely placed as to destroy all the tumor and yet spare all the surrounding brain. This, I submit, would be extremely difficult if not impossible to do. However, assuming even that it could be accomplished, it would be necessary either to carry the effect of the destructive agent deliberately into the neighboring brain tissues in cases of infiltrating tumors and thus destroy vital brain elements, or leave the infiltrating portions of the tumor behind, thus guaranteeing recurrence.

The advantage of roentgen irradiation therapy over these methods is the relatively selective destructive effect on the tumor cells, and the resistance of normal neuronal elements to the same dose of radiation. Ideally, of course, one should have an agent that would destroy the tumor completely and leave normal tissue completely unharmed. If such an agent existed, our search for the cure of cancer would have come to an end. Unfortunately, this is seldom true. However, in some cases of highly radiosensitive tumors, such cures are occasionally

*Following this treatment she had another remission lasting about 8 months. Tumor symptoms then again recurred, and she died after an attempted radical operation by another surgeon.

achieved; and some, among the tumors under discussion, belong to this group.

I believe, therefore, that now and for the foreseeable future the most promising treatment for tumors in the pineal region is radiation therapy. I am purposely not going into a discussion of the type of radiation used, since this has changed over the years both in the efficiency of the source of radiation and the accuracy of focus on the lesion. Suffice it to say that the cases with the longest follow-up obviously received the least sophisticated forms of therapy. This would indicate that some of these tumors are remarkably sensitive to radiation. As my old grandmother used to say, "If God wills it, even a broomstick can shoot."

Prior to the application of radiation therapy to the tumor itself, these patients are in urgent need of relief from increased intracranial pressure produced by the obstruction of the aqueduct. This, in my estimation, cannot be achieved adequately in the majority of cases by just a simple subtemporal decompression, and some form of shunting procedure is preferable to bring about this result.

It may be of some interest to you to review, briefly, the history of the diversion of the cerebrospinal fluid stream past an obstruction. As early as 1908 it was suggested by Anton,[2] and done by Von Bramann, that a hole be punctured in the corpus callosum, which forms the roof of the lateral ventricles (Balkenstich). This is theoretically logical and technically not difficult to perform, but due to the thickness of the corpus callosum and the relatively small and collapsible subarachnoid spaces into which the fluid escaping through this hole would have to enter in order to be reabsorbed, this method does not work.

In 1923 Mixter[21] inserted an urethroscope into the dilated lateral ventricle of a hydrocephalic child, and then, under direct vision, passed the instrument through the dilated foramen of Monro and punctured the thinned-out floor of the third ventricle with a probe inserted through the urethroscope. The communication was still functioning a few weeks afterward, when the report was published, but no follow-up appeared later.

Stookey and Scarff[27] in 1936 advocated the puncture of the thinned-out lamina terminalis by way of a right transfrontal craniotomy, to permit the cerebral fluid to pass into the roomy cisterns of the base of the brain and thus rejoin the cerebral fluid stream on its way to absorption. They took the additional precaution of puncturing the posterior wall

of the third ventricle to place this cavity in communication with the pontine cistern as well. This addition can be, I believe, theoretically dangerous and, in my experience, is not necessary. However, their approach to the lamina terminalis is direct and simple to carry out, and I am convinced that the opening produced in the floor of the ventricle in most cases remains open and continues to function.

Dandy[8] in 1945 advocated the puncture of the lamina terminalis through a temporal approach, but this was a personal preference and, insofar as I could see, had no advantages over the anterior approach.

In 1939 Torkildsen described a new method for shunting cerebral fluid around an obstruction by the insertion of a tube into a dilated lateral ventricle through a burr hole in the skull, and then leading it out over the skull but under the scalp into the subarachnoid space in the cisterna magna and upper cervical spinal canal—a method referred to previously.

Since I have a personal revulsion against leaving foreign substances of any kind permanently in the human body, and since the Stookey-Scarff procedure has worked well in my hands, I have seldom made use of the ingenious procedure of Torkildsen.

One proof of the efficacy of the third ventriculostomy, in the immediate postoperative phase at least, is the prompt relief the patient feels from the headaches and vomiting, and the relatively early subsidence of the papilledema. If a patient has only a subtemporal decompression, without a third ventriculostomy, these symptoms disappear much more slowly under the favorable effect of radiation therapy, and the decompression site bulges and is tense for a long time. Whereas, when the ventriculostomy is done and a deliberate decompression is also made, or a small defect in the skull is left perforce, the intracranial contents do not bulge through the defect, and the skin that covers the defect is soft and relaxed almost immediately, even before radiation therapy is instituted.

One might raise the question of whether a permanent communication is necessary, since it may be expected that in favorable cases the disappearance of the tumor under radiation therapy will relieve the obstruction and make the shunt superfluous. It would be difficult to answer this question categorically. It may well be that in some cases the radiation retards or arrests the growth of the tumor rather than destroys it. In this situation the shunt would be a permanently necessary ingre-

dient in the satisfactory circulation of the cerebrospinal fluid. On the other hand, if the normal diameter of the lumen of the aqueduct of Sylvius becomes reestablished, it is possible that the reduction in size of the ventricles may thicken the anterior wall of the third ventricle sufficiently to close off the artificial opening. If, on the other hand, it remains permanently open, and the circulation of the cerebral fluid utilizes both passages, I can see no harm in it. It would seem to me much less desirable, if a patient no longer needed the bypass, to have one by the way of an implanted plastic tube. This is another reason for not using the Torkildsen procedure, unless an initial puncture of the lamina terminalis should fail to do the job.

One other weakness in the course of treatment previously outlined in these cases, other than its failure to cure *all* the patients, is the use of radiation therapy on lesions that are unverified histologically. Radiotherapists are unhappy about treating unverified lesions, particularly when they are asked to apply their rays to tumors in the pineal region that could be anything from teratomas, germinomas, gliomas, and pinealomas to tuberculomas, metastatic carcinomas, or benign cysts. However, in view of the tremendous risk to the patient from attempts to obtain a biopsy, I have found all the radiotherapists with whom I have worked to be understanding and cooperative. After all, it is better to have a living patient, restored to good health, whose diagnosis lacks the stamp of certainty that the microscope provides, than it is to have beautiful microphotographs from postmortem specimens.

ACKNOWLEDGMENT

I am indebted to Dr. Mannie M. Schechter for all illustrations used in this paper, except Figure 4.

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